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(54) PROCESS FOR THE PRODUCTION OF VITAMIN C

(71) We POLITECHNIKA SLASKA IM.W. PSTROWSKIEGO, Gliwice, Konarskiego 23, Poland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a method of manufacturing ascorbic acids, i.e. vitamin C.

Known processes for the production of various isomers of l-ascorbic acid, i.e. vitamin C, from 2-keto-hexonic acids, or from esters of ketonoacetal or acetal derivatives thereof are carried out by direct heating of solutions of the compounds mentioned above with solutions of strong acids such as for example hydrochloric acid.

Other known processes for the production of ascorbic acids from 2-keto-hexonic acids or their ketonoacetal or acetal derivatives are carried out firstly by acid-catalyzed esterification of the starting materials and then by base-catalyzed lactonization and enolization of the esters thus obtained. In this two-stage process for the production of ascorbic acids, acid cation-exchange resins are used as catalysts for the esterification steps.

There is also known a process in which anion-exchange resins are used as basic agents for effecting lactonization and enolization of 2-keto-hexonic acid esters.

These known processes of producing ascorbic acids are, however, not free of disadvantages such as high contamination of post-reaction solutions with attendant laborious and time-consuming operations, involving such poor yields that they lacked commercial utility.

An object of the present invention is to obviate or mitigate the defects and shortcomings of former processes.

It has now been found that 2-keto-hexonic acids and certain derivatives thereof can be converted in one step into ascorbic acid by treating the hexonic acid or derivative thereof with a cation exchange resin.

According to the present invention there is provided a method of manufacturing ascorbic acid, comprising enolising and lactonising a compound selected from 2-keto-hexonic acids, esters thereof and acetal and ketono-acetal derivatives thereof by heating a solution thereof with a cation exchange resin.

In carrying out in practice the method according to the present invention, the reactions involved are lactonization and enolization, optionally with prior hydrolysis.

The term "2-keto-hexonic acids" is used herein and in the claims to include 2-keto-L-gulonic acid, 2-keto-L-idonic acid, and 2-keto-D-gluconic acid.

The process according to the present invention enables relatively pure post-reaction solutions to be obtained since no additional soluble chemical reagents need be introduced into the reaction solution. Moreover, the process according to the present invention is not laborious and it can be fully automated. It does not involve formation of by products or decomposition products and hence it is characterised by a good yield.

The process of producing ascorbic acids according to the invention may comprise single-stage heating of a 2-keto-hexonic acid, or ester or acetal or ketonoacetal derivatives thereof, in an aqueous solution, of in an organic solvent solution, in the presence of cation-exchange resin in an acid or salt form, or in the presence of a mixture of acid and salt cation exchange-resins.

Strong acid cation exchangers, for example, polystyrene-sulphonic exchangers known as Wofatit KPS, Zerolit 225, Dow-50, "Zerolit" and "Dow" are Registered Trade Marks) and others, can be advantageously used as cation-exchange resins.

The said resins can be used in acid form (also called hydrogen form) or in salt-form (called also metallic form). In the latter case it is advantageous to impregnate the ion-exchanger with alkali metal ions e.g. with lithium, sodium, potassium, rubidium or cesium, either alone or in mixtures thereof. It is also profitable to use combined salt-acid forms, comprising an acid agent, for example, in amount of about 5.95%. Although

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ascorbic acid is the essential component of all post-reaction mixtures obtained in the process according to the invention, it is not necessarily the sole component of these solutions, since a portion of unreacted raw material may also be included therein. Unreacted raw material may be recycled on separation thereof.

The chemical form of this portion of the unreacted raw material depends on the type of solvent used and on the particular processing applied. It also affects the further isolation of ascorbic acid from the post-reaction mixture by fractional crystallization induced by means of evaporation and inspissation of the solution or by cold treatment or by precipitation with another solvent.

If water is used as a solvent, then, besides ascorbic acid, 2-keto-hexonic acid is also present in the post-reaction solution, as also occurs when non-esterifying organic solvents are used. When using an alcohol as a reaction medium, esters can also be obtained as by products in the post-reaction mixtures.

Hence the composition of the post-reaction mixtures can be regulated in order to effect a suitable distribution of post-reaction components. For example, 2-keto-L-gulonic acid crystallises first from a mixture of L-ascorbic acid and 2-keto-L-gulonic acid; on the other hand, from a mixture of L-ascorbic acid and the ethyl ester of 2-keto-L-gulonic acid L-ascorbic acid crystallises first.

In order to obtain an ester of 2-keto-hexonic acid along with ascorbic acid, it is advantageous to carry out this process in an alcoholic medium in the presence of a cation-exchange resin in acid form, previously dehydrated. If acetal or ketonoacetal derivatives of 2-keto-hexonic acid are used as starting materials it is advantageous to carry out this process firstly in the presence of a hydrated resin in order to enable the acetal or ketonoacetal groups to be hydrolyzed, and then in the presence of a dehydrated resin in water-free conditions.

The said dehydration of a cation-exchange resin can be performed for example by drying a resin by means of zeolite molecular sieves 3A, 4A, 5A, 13X and others.

The following examples are given to illustrate the present invention in more detail.

EXAMPLE I

A flask of 2-litres capacity, furnished with an agitator, was charged with 600 ml of the cation exchange resin Zerolit 225 ("Zerolit" is a Registered Trade Mark) in the potassium form. Then 1 litre of a 20% aqueous solution of diacetone-2-keto-1-gulonic acid was added. After generating a nitrogen atmosphere above the solution, the whole content was heated under stirring for a 7-hour period at a temperature somewhat lower than the boiling point. When the heating period was coming to an end, the solution contained about 78% of 1-ascorbic acid in relation to the total acids content. After filtering off the resin and washing it with water fully to stop the acid reaction, the post-reaction solution was inspissated by distilling off water at a temperature of about 60° under somewhat diminished pressure in order to obtain a consistency of a syrup.

After grafting with crystals of 2-keto-L-gulonic acid, the syrup was left for some days in a refrigerator in order to obtain total crystallisation of 2-keto-L-gulonic acid. After centrifuging the product and washing it with methyl alcohol, the post-crystallisation solution was grafted with crystalline L-ascorbic acid and left for some days in order to complete its crystallisation. After crushing the nearly-congealed crystalline mass, it was centrifuged while washing it with methyl alcohol.

70 g of L-ascorbic acid were obtained, which amounts to about 60% of the theoretical yield. The melting point of the product obtained was in the temperature range 186—188°C. In order to increase the yield, all solutions obtained from the washing of crystals were mixed together, liberated from methyl alcohol by evaporation and the after-crystallisation residue was mixed with crystalline 2 - keto - L - gulonic acid (being previously regenerated), dissolved in 400 ml of water, mixed with the cation-exchanger in potassium form previously used, heated, evaporated and crystallised in the same manner as given above. An additional amount of 23 g of L-ascorbic acid was recovered, with a melting point in the range of 184—187°C. The total yield of L-ascorbic acid (vitamin C) obtained was about 80% of the theory.

EXAMPLE II

A batchwise process was carried out in the following manner. Into a round-bottomed flask, with a volume of 250 ml, 50 ml of tert.-butyl alcohol were introduced and 4 g of 2-keto-L-gulonic acid were dissolved therein. Then 30 g of polystyrene-sulphonic cation exchanger Wofatit KPS in hydrogen form were added. The said cation exchange was previously dehydrated in a separate vessel by means of an inorganic molecular sieve of Zeolite 5A type. The reaction mixture was heated in a water bath for six hours, cooled and centrifuged to separate the cation exchanger.

The clear, almost colourless solution obtained was evaporated to a small volume, cooled and submitted to crystallisation. Crystalline ascorbic acid of slight yellowish colouration was obtained therefrom in a yield of about 3.3 g.

EXAMPLE III

A continuous process was carried out in the following manner. A glass column, hav-

ing a diameter of 20 mm, a height of 500 mm, provided with a heating jacket maintaining a constant temperature of 80°C., was charged with the cation exchanger Zerolit 225 ("Zerolit" is a Registered Trade Mark) in hydrogen form, being previously dried by means of the molecular sieve 4A.

Then a solution containing 10 g of 2-keto-L-gulonic acid in 100 ml of dioxane was introduced into the column and passed in stages therethrough with such a velocity as to retain this solution in the column for about 1 hour. A clear and almost colourless effluent was collected and evaporated to a small volume at a temperature of about 40°C. without access of air. After cooling, the crystals obtained were filtered yielding about 8.2 g of ascorbic acid.

The ascorbic acid obtained is suitable for pharmacological purposes directly or after additional recrystallisation from water.

EXAMPLE IV

20 g of diacetone - 2 - keto - L - gulonic acid were dissolved in 200 ml of ethyl alcohol, containing 0.5 per cent of water. The solution was heated up to about 80°C, and passed in stages through a column (dimensions of the column — 15 mm×300 mm) heated to 75°C., packed with air-dried cation exchange resin Zerolit 225 ("Zerolit" is a Registered Trade Mark), with such a velocity as to obtain contact of every particle of the resin with the solution for about 15 minutes.

The effluent from the column was introduced into a second column (dimensions 25 mm×1000 mm) heated to a temperature of about 75°C, and packed with anhydrous cation-exchanger Zerolit 225 ("Zerolit" is a Registered Trade Mark). The solution was passed through with such a velocity as to obtain the contact of every particle of the resin with the solution for a two hour period.

The effluent was collected and was evaporated to a volume of about 40 ml and then frozen. 10 g of L-ascorbic acid were obtained, which amounts to about 90 per cent of the theoretical yield. The melting point of the product was 184—185°C. The first column was suitable for immediate working on a subsequent batch, while the packing of the second column required to be carefully dehydrated before use for a subsequent batch.

WHAT WE CLAIM IS:—

1. A method of manufacturing ascorbic acid, comprising enolising and lactonising a compound selected from 2-keto-hexonic acids, esters thereof and acetal and ketonoacetal derivatives thereof by heating a solution thereof with a cation exchange resin.

2. A method as claimed in claim 1, wherein the said compound is a 2-keto-hexonic acid or an ester thereof, the cation exchange resin is in a dehydrated form, and the solvent is organic.

3. A method as claimed in claim 1, wherein the said compound is an acetal or ketonoacetal derivative of a 2-keto-hexonic acid, and reaction is effected in a first step in the presence of a hydrated cation-exchange resin and in a second step in the presence of a dehydrated cation-exchange resin.

4. A method as claimed in any one of the preceding claims wherein the cation exchange resin is in acid form.

5. A method as claimed in any one of claims 1 to 4, wherein the cation exchange resin is in salt form.

6. A method as claimed in any one of claims 1 to 4, wherein the cation exchange resin comprises a mixture of acid and salt forms.

7. A method as claimed in claim 5 or claim 6, wherein the cation exchange resin in salt form contains an alkali metal cation.

8. A method as claimed in any one of the preceding claims, wherein a post-reaction solution is obtained from which ascorbic acid and a said compound are separated by fractional crystallisation and the separated said compound is used in a subsequent manufacture of ascorbic acid.

9. A method of manufacturing ascorbic acid according to claim 1 and substantially as hereinbefore described.

10. A method of manufacturing ascorbic acid, according to any one of the Examples.

11. Ascorbic acid whenever manufactured by the method claimed in any one of the preceding claims.

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